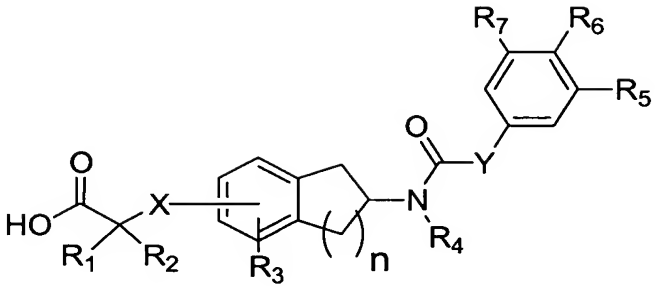
CLAIMS

1. A compound of Formula I



Formula I

or a pharmaceutically acceptable salt, C $_{1-6}$ ester or C $_{1-6}$ amide thereof, wherein

each of R_1 and R_2 is independently H, C $_{1-6}$ alkyl, $(CH_2)_mNR_aR_b$, $(CH_2)_mOR_8$, $(CH_2)_mNH(CO)R_8$, or $(CH_2)_mCO_2R_8$, where each of R_a, R_b, and R_8 is independently H or C $_{1-6}$ alkyl, or R_1 and R_2 taken together with the carbon atom to which they are attached are a C $_{3-7}$ cycloalkyl;

m is between 1 and 6;

n is 1 or 2;

X is O or S; wherein X is at the 5 or 6 position when n is 1; and wherein X is at the 6 or 7 position when n is 2;

R_3 is H, phenyl, C $_{1-3}$ alkoxy, C $_{1-3}$ alkylthio, halo, cyano, C $_{1-6}$ alkyl, nitro, NR_9R_{10}, $NHCOR_{10}$, $CONHR_{10}$; and $COOR_{10}$; and R_3 is ortho or meta to X;

R_4 is H or -(C $_{1-5}$ alkylene)R_{15}, where R_{15} is H, C_{1-7} alkyl, [di(C $_{1-2}$ alkyl)amino](C $_{1-6}$ alkylene), (C $_{1-3}$ alkoxyacyl)(C $_{1-6}$ alkylene), C $_{1-6}$ alkoxy, C $_{3-7}$ alkenyl, or C $_{3-8}$ alkynyl, wherein R_4 has no more than 9 carbon atoms; R_4 can

also be -(C $_{1-5}$ alkylene)R_{15} wherein R_{15} is C $_{3-6}$ cycloalkyl, phenyl, phenyl-O-, phenyl-S-, or a 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;

Y is NH, NH-CH_2, and O;

each of R_5 and R_7 is independently selected from H, C $_{1-6}$ alkyl, halo, cyano, nitro, COR_{11}, $COOR_{11}$, C $_{1-4}$ alkoxy, C $_{1-4}$ alkylthio, hydroxy, phenyl, $NR_{11}R_{12}$ and 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;

R_6 is selected from C $_{1-6}$ alkyl, halo, cyano, nitro, COR_{13}, $COOR_{13}$, C $_{1-4}$ alkoxy, C $_{1-4}$ alkylthio, hydroxy, phenyl, $NR_{13}R_{14}$ and 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;

in addition, either R_5 and R_6 or R_6 and R_7 may be taken together to be a bivalent moiety, saturated or unsaturated, selected from $-(CH_2)_3-$, $-(CH_2)_4-$, and $(CH_{1-2})_pN(CH_{1-2})_q$,

p is 0-2 and q is 1-3, where the sum (p + q) is at least 2;

each of R_9 and R_{10} is independently C $_{1-6}$ alkyl;
each of R_{11}, R_{12}, R_{13} and R_{14} is independently H or C $_{1-6}$ alkyl;

wherein each of the above hydrocarbyl and heterocarbyl moieties may be substituted with between 1 and 3 substituents independently selected from F, Cl, Br, I, amino, methyl, ethyl, hydroxy, nitro, cyano, and methoxy.

2. A compound of claim 1, wherein one of R_1 and R_2 is methyl or ethyl.

3. A compound of claim 2, wherein each of R_1 and R_2 is methyl.

4. A compound of claim 1, wherein R_1 and R_2 taken together are cyclobutyl or cyclopentyl.

5. A compound of claim 1, wherein R_3 is H.

6. A compound of claim 1, wherein R_3 is C_{1-3} alkoxy, C_{1-3} alkylthio, halo, cyano, C_{1-6} alkyl, nitro, NR_9R_{10}, $NHCOR_{10}$, $CONHR_{10}$; or $COOR_{10}$.

7. A compound of claim 1, wherein R_4 is H or C_{2-7} alkyl.

8. A compound of claim 7, wherein R_4 is H or C_{2-5} alkyl.

9. A compound of claim 8, wherein R_4 is ethyl.

10. A compound of claim 8, wherein R_4 is H.

11. A compound of claim 1, wherein n is 1.

12. A compound of claim 1, wherein n is 2.

13. A compound of claim 1, wherein Y is $NH\text{-}CH_2$.

14. A compound of claim 1, wherein Y is NH.

15. A compound of claim 1, wherein X is S.

16. A compound of claim 1, wherein X is O.

17. A compound of claim 1, wherein at least one of R_5 and R_7 is H.

18. A compound of claim 17, wherein R_6 is C $_{1-4}$ alkyl, halomethoxy, halomethylthio, or di(C $_{1-3}$ alkyl)amino.

19. A compound of claim 18, wherein R_6 is trifluoromethoxy, difluoromethoxy, trifluoromethyl, trifluoromethylthio, t-butyl, isopropyl, or dimethylamino.

20. A compound of claim 3, wherein R_3 is H, R_4 is C $_{2-7}$ alkyl, and Y is NH.

21. A compound of claim 20, wherein X is S.

22. A compound of claim 20, wherein n is 1.

23. A compound of claim 20, wherein n is 2.

24. A compound of claim 20, wherein R_4 is C $_{2-5}$ alkyl.

25. A compound of claim 24, wherein R_4 is ethyl.

26. A compound of claim 20, wherein R_6 is trifluoromethoxy, difluoromethoxy, trifluoromethyl, trifluoromethylthio, t-butyl, isopropyl, or dimethylamino.

27. A compound of claim 1, wherein each of R_1 and R_2 is independently H, C $_{1-6}$ alkyl, $(CH_2)_mNR_aR_b$, or $(CH_2)_mOR_8$, where each of R_a, R_b, and R_8 is independently H or C $_{1-6}$ alkyl;

m is between 1 and 6;

n is 1 or 2;

X is O or S; wherein X is at the 5 or 6 position when n is 1; and wherein X is at the 6 or 7 position when n is 2;

R_3 is H, phenyl, C $_{1-3}$ alkoxy, C $_{1-3}$ alkylthio, halo, C $_{1-6}$ alkyl, or NR_9R_{10}, and R_3 is ortho or meta to X;

R_4 is H or -(C $_{1-5}$ alkylene)R_{15}, where R_{15} is H, C_{1-7} alkyl, [di(C $_{1-2}$ alkyl)amino](C $_{1-6}$ alkylene), (C $_{1-3}$ alkoxyacyl)(C $_{1-6}$ alkylene), C $_{1-6}$ alkoxy, or C $_{3-7}$ alkenyl, wherein R_4 has no more than 9 carbon atoms;
R_4 can also be -(C $_{1-5}$ alkylene)R_{15} wherein R_{15} is C $_{3-6}$ cycloalkyl, phenyl, phenyl-O-, phenyl-S-, or a 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;

Y is NH or $NHCH_2$;

each of R_5 and R_7 is independently selected from H, C $_{1-6}$ alkyl, halo, COR_{11}, $COOR_{11}$, C $_{1-4}$ alkoxy, C $_{1-4}$ alkylthio, hydroxy, and $NR_{11}R_{12}$;

R_6 is selected from C $_{1-6}$ alkyl, halo, COR_{13}, $COOR_{13}$, C $_{1-4}$ alkoxy, C $_{1-4}$ alkylthio, phenyl, $NR_{13}R_{14}$ and 5-6 membered heterocyclyl with between 1 and 2 heteroatoms selected from N, O, and S;

each of R_9 and R_{10} is independently C $_{1-6}$ alkyl;
each of R_{11}, R_{12}, R_{13} and R_{14} is independently H or C $_{1-6}$ alkyl;

wherein each of the above hydrocarbyl and heterocarbyl moieties may be substituted with between 1 and 3 substituents independently selected from F, Cl, amino, methyl, ethyl, hydroxy, and methoxy.

28. A compound of claim 1, selected from:
2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;
2-{2-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{2-[1-Ethyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[1-pentyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-{2-[1-Ethyl-3-(4-isopropylphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[1-pentyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{2-[3-(4-Dimethylaminophenyl)-1-ethylureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[1-(3-methylbutyl)-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{2-[3-(4-Isopropylphenyl)-1-(3-methylbutyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methy-2-{2-[1-pent-4-enyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methoxy-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-chloro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-bromo-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methyl-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid; and

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-trifluoromethoxy-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid.

29. A compound of claim 1, selected from

2-Methyl-2-{2-[1-hexyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}propionic acid ;

2-{2-[3-(4-Dimethylaminophenyl)-1-pentylureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-Methyl-2-{2-[1-propyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-Methyl-2-{2-[1-butyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-{2-[3-(4-Isopropylphenyl)-1-(3-pentyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{2-[3-(4-*tert*-Butylphenyl)-1-(3-pentyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-[2-(3-(Biphenyl-4-yl-1-pentylureido)indan-5-ylsulfanyl]-2-methylpropionic acid;

2-{2-[3-(4-Isopropylphenyl)-1-(3-hexyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[1-butyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methoxy-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-chloro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-bromo-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methyl-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid; and

2-Methyl-2-{2-[1-hexyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid.

30. A compound of claim 1, selected from:

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[3-(4-Trifluoromethoxyphenyl)ureido]-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{2-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-methyl-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid;

2-{2-[1-Ethyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid; and

2-Methyl-2-{2-[1-propyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid.

31. A compound of claim 1, selected from:

2-{2-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-{2-[1-Ethyl-3-(4-trifluoromethylsulfanylphenyl)ureido]indan-5-ylsulfanyl}-2-methylpropionic acid;

2-Methyl-2-{2-[1-propyl-3-(4-trifluoromethoxyphenyl)ureido]indan-5-ylsulfanyl}propionic acid; and

2-{6-[1-Ethyl-3-(4-trifluoromethoxyphenyl)ureido]-3-fluoro-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl}-2-methylpropionic acid.

32. A pharmaceutical composition, comprising a compound of claim 1, 20, 27, 28, 30, or 31.

33. A method for treating or inhibiting the progression of a PPAR-alpha mediated disease, said method comprising administering to a patient in need of treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1, 20, 27, 28 or 31, wherein said PPAR-alpha mediated disease is selected from impaired glucose tolerance, hyperinsulinemia, hyperglycemia, insulin resistance, and early, intermediate or late Type II diabetes (NIDDM), and complications thereof.

34. A method of claim 33, wherein said complication is selected from retinopathy, nephropathy, and neuropathy.

35. A method of claim 33, wherein said PPAR-alpha mediated disease is selected from impaired glucose tolerance, insulin resistance, hyperglycemia, hyperinsulinemia, and early Type II diabetes, and complications thereof.

36. A method of claim 33, wherein said PPAR-alpha mediated disease is selected from intermediate or late Type II diabetes, and complications thereof.

37. A method of claim 33, wherein said compound of claim 1, 20, 27, 28, or 31 is a first anti-diabetic agent, and wherein said method further comprises the step of administering to the patient a jointly-effective amount of a second anti-diabetic agent.

38. A method of claim 37, wherein said second anti-diabetic agent is selected from PPAR alpha and PPAR gamma modulating agents.

39. A method of claim 37, wherein said second anti-diabetic agent is insulin.

40. A method of claim 33, further comprising the step of administering a jointly-effective amount of a third pharmaceutically active agent.

41. A method of claim 40, wherein said third pharmaceutically active agent is selected from an anti-diabetic agent, a lipid lowering agent, and a blood-pressure lowering agent.

42. A method both for treating or inhibiting the progression of a PPAR-alpha mediated disease and for treating or inhibiting the progression of dyslipidemia, said method comprising administering to a patient in need of treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1, 20, 27, 28 or 31, wherein said PPAR-alpha mediated disease is selected from impaired glucose tolerance, hyperinsulinemia, insulin resistance, and early, intermediate or late Type II diabetes (NIDDM), and complications thereof.

43. A method of claim 42, wherein said composition consists essentially of a compound of claim 1, 20, 27, 28, or 31.